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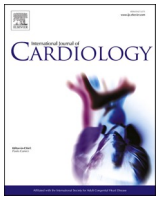

Review

Contemporary management of acute pulmonary embolism

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ABSTRACT

Acute pulmonary embolism (PE) is one of the leading causes of in-hospital mortality and the third more frequent cause of cardiovascular mortality. The optimal management of PE patients is a clinical conundrum since the spectrum of PE manifestations varies largely depending on clinical and hemodynamic features. According to international guidelines, systemic thrombolysis ranks as first-line treatment for high-risk PE complicated by hemodynamic instability. However, a not negligible proportion of PE patients present contraindications to systemic thrombolysis. Among hemodynamically stable patients with right ventricular dysfunction ("intermediate risk" PE), anticoagulation alone remains the standard treatment but is still associated with relevant risk. Novel interventional techniques including catheter-directed thrombolysis, mechanical thrombectomy, and hybrid approaches have been developed to facilitate reperfusion while mitigating the risk of bleeding. In this review, we provide a comprehensive and contemporary overview of pharmacological and interventional treatments for PE, moving from clinical evidence to practical recommendations and future directions.

1. Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE) ranks as the third cause of cardiovascular mortality, following myocardial infarction and stroke [1]. Despite advancements in the risk stratification, diagnostic work-up and clinical management, PE remains responsible for 6.5 deaths per 100.000 individuals in Western countries [2,3].

PE is usually characterized by the dislodgement of fragments of venous thrombus occluding one or more pulmonary arterial vessels. In rare cases, it may consist of local in situ thrombosis. According to the Virchow's triad at least one of the following mechanisms are causal factors for venous thrombosis: vessel wall damage, flow stasis, and hypercoagulable state [4].

The spectrum of PE manifestations may vary largely depending on the extension of thrombus dislodgment and the presence of pre-existing cardiopulmonary diseases. Vascular occlusion by embolic material triggers the release of vasoconstrictor mediators, increasing pulmonary arterial pressure. The pulmonary vascular resistance increase might result in right ventricular (RV) dilation and increased RV wall tension. RV pressure overload leads to oxygen supply-demand imbalance, causing RV ischemia and dysfunction. RV dysfunction may lead to a decrease of left ventricular (LV) preload, which can be further impaired by the leftward shift of the interventricular septum. This process can ultimately lead to cardiogenic shock and death [1]. Additionally, the presence of hypoperfused alveoli increases alveolar dead space, resulting in ventilation/perfusion (V/Q) mismatch and hypoxemia. Low oxygen saturation stimulates tachypnoea, potentially leading to

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compensatory hypocapnia [1].

2. Risk stratification

The 2019 European Society of Cardiology (ESC) guidelines on PE endorse a multiparametric risk stratification scheme to determine the optimal therapeutic approach in each individual patient [4]. Hemodynamically stable patients without signs or symptoms of RV dysfunction and cardiac troponin increase are classified as low-risk patients with a favourable prognosis with anticoagulant treatment (Fig. 1). The presence of one of either RV dysfunction/dilation at imaging tests (echocardiography and/or computed tomography) or troponin elevation identifies patients as intermediate-low risk. Conversely, the presence of clinical parameters of PE severity such as both RV dysfunction and elevated cardiac troponin levels (intermediate-high risk patients) or hemodynamic instability (high-risk patients), is associated with a worse prognosis (Fig. 1) [5].

3. The pulmonary embolism response team (PERT)

Given the complexity of the disease in its various manifestations and the range of interventional and/or pharmacological strategies, the implementation of the pulmonary embolism response team (PERT) has been established across multiple centres to provide rapid, individualized, and multidisciplinary expert-based care for PE patients (Fig. 2). The ESC guidelines on PE recommend the creation of a PERT with a class IIa of recommendation (Level of Evidence [LOE] C) [5].

While current international guidelines and consensus documents endorses the use of interventional therapies for high-risk or intermediate-risk patients with clinical deterioration or lack of improvement, the management of normotensive intermediate-risk patients requires a case-by-case assessment [6]. To this regard, the PERT plays a crucial role by providing the necessary clinical expertise in such cases [7–10].

4. Treatment of pulmonary embolism

4.1. Systemic thrombolysis

High-risk patients with PE presenting with cardiac arrest or cardiogenic shock require immediate reperfusion therapy. In this patient population, current international guidelines recommend systemic thrombolysis in the absence of contraindications (Table 1), with a class I

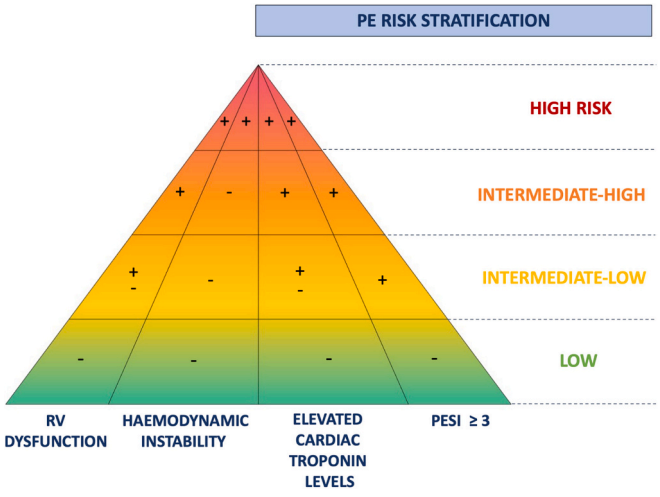

Fig. 1. The European Society of Cardiology risk stratification of PE severity. Abbreviations: RV = right ventricle; PESI = pulmonary embolism severity index.

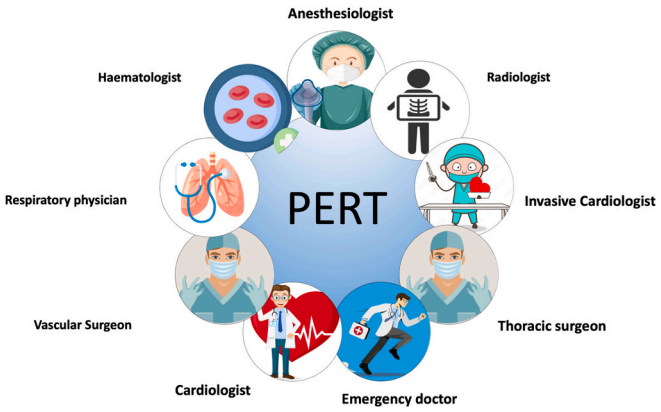

Fig. 2. The pulmonary embolism response team (PERT).

of recommendation (LOE B) [5]. Intravenous administration of thrombolytic agents (such as alteplase) activates plasminogen to plasmin, thereby accelerating the lysis of thrombo-embolic fragments. In the recent randomized FORPE trial, the comparative efficacy and safety of non-immunogenic staphylokinase was compared with alteplase in 155 patients with massive PE and RV dysfunction. Non-immunogenic staphylokinase met non-inferiority for the primary composite endpoint of 7-day all-cause mortality (odds ratio [OR]: 0.75, 95 % confidence interval [CI]: 0.11–4.49), with an excellent safety profile [11].

The class I recommendation for systemic thrombolysis is supported by a study-level meta-analysis encompassing fifteen trials for a total of 2057 patients with intermediate- and high-risk PE published over a time span of almost 45 years [12]. Compared with heparin, thrombolytic therapy was associated with significantly lower risk of mortality (OR: 0.59, 95 % CI: 0.36–0.96). After the exclusion of studies of high-risk PE, the mortality risk did not differ between the two groups (OR: 0.64, 95 % CI: 0.35–1.17). Systemic thrombolysis was associated with higher risks of major bleeding (OR: 2.91, 95 % CI: 1.95–4.36) and fatal or intracranial bleeding (OR: 3.18, 95 % CI: 1.25–8.11) compared with heparin alone [12]. The observed mortality benefit favouring systemic thrombolysis in this meta-analysis was mainly driven by a small study published in 1995 involving only 8 high-risk patients. In this study, patients were randomized to receive either thrombolysis with streptokinase combined with heparin or heparin alone. In the heparin-only arm, all patients died within 1 to 3 h of presentation. Conversely, in the thrombolysis arm, all patients survived, and none developed pulmonary hypertension at the one-year follow-up [13]. Moreover, the heterogeneity among the studies included in the metaanalysis was significant, with an I^2 index of 47 % for the primary endpoint of overall mortality.

The PEITHO trial (*Pulmonary EmbolIsm THrOmbolysis*) randomized 1006 normotensive patients with intermediate risk PE to weight-adapted tenecteplase plus heparin versus placebo plus heparin. Death or hemodynamic decompensation occurred in 13 of 506 patients (2.6 %) in the tenecteplase group and 28 of 499 (5.6 %) in the placebo group (OR: 0.44; 95 % CI: 0.23–0.87; $P = 0.02$). Between randomization and day 7, a total of 6 patients (1.2 %) in the tenecteplase group and 9 (1.8 %) in the placebo group died ($P = 0.42$). Extracranial bleeding occurred in 32 patients (6.3 %) in the tenecteplase group and 6 patients (1.2 %) in the placebo group ($P < 0.001$). Stroke occurred in 12 patients (2.4 %) in the tenecteplase group and was hemorrhagic in 10 patients; 1 patient (0.2 %) in the placebo group had a stroke, which was haemorrhagic ($P = 0.003$). By day 30, a total of 12 patients (2.4 %) in the tenecteplase group and 16 patients (3.2 %) in the placebo group had died ($P = 0.42$) [14].

The increased risk of bleeding [14], including intracranial haemorrhages, prompted a decrease in clinician confidence regarding the use of full-dose systemic fibrinolysis, especially in patients without hemodynamic instability. Consequently, this treatment is currently indicated only in high-risk PE patients with hemodynamic shock, despite having

Table 1
Absolute and relative contraindications to systemic thrombolysis. Abbreviations: RCP = cardiopulmonary resuscitation, INR = international normalized ratio, PT = prothrombin time.

Absolute contraindications
▪ Prior intracranial haemorrhage
▪ Known structural cerebral vascular lesion
▪ Known malignant intracranial neoplasm
▪ Ischemic stroke within 3 months
▪ Active bleeding or bleeding diathesis (excluding menses)
▪ Significant closed-head trauma or facial trauma within 3 months
▪ Any known bleeding diathesis or internal bleeding

Relative contraindication
▪ Severe uncontrolled hypertension on presentation (SBP >180 mmHg or DBP >110 mmHg)
▪ History of ischemic stroke >3 months prior
▪ Traumatic or prolonged (>10 min) CPR or major surgery <3 weeks
▪ Recent (within 2 to 4 weeks) internal bleeding
▪ Non-compressible vascular punctures
▪ Prolonged cardio-pulmonary resuscitation
▪ Recent invasive procedure within 1 week
▪ For streptokinase/anistreplase – Prior exposure (>5 days ago) or prior allergic reaction to these agents
▪ Pregnancy
▪ Active peptic ulcer
▪ Pericarditis or pericardial fluid
▪ Current use of anticoagulant (e.g., warfarin sodium) inducing elevated INR >1.7 or PT >15 s
▪ Age >75 years
▪ Diabetic retinopathy

been investigated mainly in intermediate PE individuals. Finally, the criteria used to select PEITHO patients based solely on RV dilation and positive troponin appeared insufficient to identify a higher-risk population. This is demonstrated by the low number of events (primary outcome rate 5.6 %) in the control group and the very low fatality rate in both groups. A subsequent post-hoc analysis of PEITHO revealed that incorporating additional clinical criteria, such as systolic blood pressure $\leq$ 110 mmHg, respiratory rate > 20 breaths/min (or, as a surrogate, hypoxemia on room air), or chronic heart failure, identified a patient subgroup at higher risk of adverse events. These patients may therefore experience a greater absolute risk reduction if treated with early reperfusion [15].

4.2. Interventional treatment of PE

In the last decade, catheter-based interventions have emerged as appealing options for intermediate and high-risk PE aimed at reducing RV pressure overload by affecting the pulmonary thrombotic burden without excessive bleeding risk, particularly intracranial bleeding [5].

The 2019 ESC guidelines recommend (class IIa, LOE C) reperfusion therapy using catheter-based interventions for intermediate-high and high-risk patients who have absolute contraindications to systemic thrombolysis. Additionally, interventional therapies are also indicated (class IIa, LOE B) for patients experiencing hemodynamic deterioration after systemic thrombolysis or during anticoagulation therapy [5]. These novel interventional techniques (Fig. 3) encompass catheter-directed thrombolysis (CDT), mechanical thrombectomy and pharmaco-mechanical techniques (Rheolytic thrombectomy) [16].

4.2.1. Catheter-directed thrombolysis

Catheter-directed thrombolysis encompasses endovascular thrombolysis alone or in association with ultrasound-assisted catheter-directed thrombolysis (USAT). CDT without ultrasound consists of positioning a catheter (usually a 4-to-5 Fr catheter, such as AngioDynamics Inc., Latham, NY, or Cragg-McNamara, Medtronic, Minneapolis, MN), into the pulmonary artery under fluoroscopic guidance. This catheter delivers a local thrombolytic drug directly to the surface of the thrombus. The thrombolytic agent is usually infused at a rate of 1-to-2 mg/h over a period of 6-to-24 h while systemic coagulation is implemented and serially monitored during the treatment.

USAT is a technique that combines the local administration of a thrombolytic agent with low-intensity ultrasound waves. Ultrasound induces changes in fibrin architecture, facilitating thrombolysis. The primary system for USAT is the EKOS® or EkoSonic endovascular system, used for treating PE, DVT, and arterial occlusion. The EKOS system includes a 6F infusion catheter, an ultrasound core wire, and a control

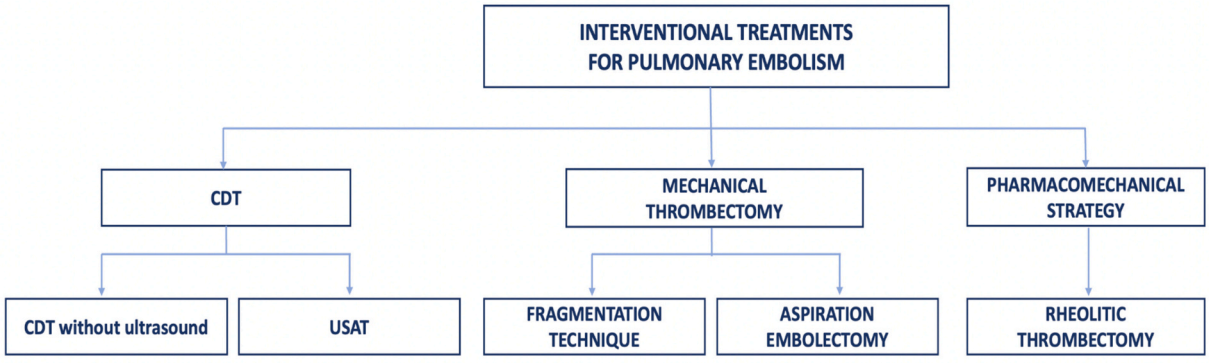

Fig. 3. Classification of interventional treatments for PE. Abbreviations: CDT = catheter-directed thrombolysis, USAT = ultrasound-assisted thrombolysis.

unit. Compared with systemic thrombolysis, USAT employs a lower total dose of the administered thrombolytic agent. However, evidence on CDT is still limited to non-randomized observational studies, small single-arm prospective studies, and small randomized trials examining surrogate and radiological outcomes [17] (Fig. 4). The ULTIMA trial is a prospective, randomized trial investigating the reduction of RV/LV ratio assessed by echocardiography in PE patients who received CDT plus anticoagulant therapy versus anticoagulant therapy alone. Patients who received CDT had a faster recovery of RV/LV ratio without bleeding risk trade-off compared with anticoagulation alone [18].

The SEATTLE II trial is a prospective, single-arm study which enrolled 150 patients with massive (i.e. high-risk) ($n = 31$) or sub-massive (i.e. intermediate-high risk) PE ($n = 119$) which demonstrated a significant reduction in RV/LV ratio by computed tomography (CT)-scan after USAT. Post-procedural systolic pulmonary artery pressure (PAP) decreased from 51.4 mmHg to 36.9 mmHg. There was a single GUSTO severe bleeding event and 15 GUSTO moderate bleeding events in the study cohort [19].

The SUNSET sPE is a prospective, randomized trial which assessed the angiographic thrombotic burden, evaluated by the Miller score at CT-scan. The study randomized 81 patients with intermediate-risk PE to low-dose USAT or CDT without ultrasound. Follow-up CT was performed 48 h after treatment to assess the reduction in thrombus burden. Also in light of the small sample size of the trial, the authors could not find any difference in the mean Miller score between the two groups using comparable mean lytic dose and treatment duration [20].

The optimal thrombolytic dose for USAT remains uncertain, with studies such as OPTALYSE suggesting equivalence between different regimens for RV unloading, but a dose-dependent response for PAP and clot burden reduction [21]. In this prospective, multicenter trial, hemodynamically stable patients with confirmed intermediate-risk pulmonary embolism by CT were randomized into four parallel groups to receive USAT with varying tPA doses, ranging from 4 to 12 mg per lung, and infusion durations from 2 to 6 h. The four regimens included 4 mg per lung over 2 h, 4 mg per lung over 4 h, 6 mg per lung over 6 h, and 12 mg per lung over 6 h. The primary efficacy endpoint was the reduction in the RV/LV diameter ratio, assessed by CT angiography, with a secondary endpoint of reduced embolic burden measured by the refined modified Miller score 48 h after the initiation of USAT. The results indicated significant improvements in the RV/LV diameter ratio across all groups, with reductions of 0.40 (24 %), 0.35 (22.6 %), 0.42 (26.3 %), and 0.48 (25.5 %), respectively, each with $p = 0.0001$, alongside a substantial reduction in embolic burden across all treatment arms. Major bleeding occurred in 4 % of patients, with two cases of intracranial haemorrhage, one of which was attributed to tPA administration via USAT. This study supports the efficacy and safety of low-dose, short-duration USAT regimens in achieving significant clinical improvement in RV function and thrombus reduction in intermediate-risk PE [21]. However, since there was no placebo group and no observed dose-response relationship, a possible interpretation is that the improvement in RV dimension and Miller score simply reflects the natural course of PE, rather than any effect of CDT.

Preliminary findings from the large observational KNOCOUT PE registry report lower bleeding rates (approximately 2.5 %) with USAT than previously reported, suggesting a positive signal regarding the safety of this approach [16].

4.2.1.1. Ongoing trials. In the ongoing, randomized, parallel-design BETULA trial, a low-dose CDT (4 mg or 8 mg alteplase per catheter over a 2-hour period using the Uni-Fuse system) is compared with heparin therapy alone in 60 patients with intermediate-risk PE and RV dysfunction. The primary endpoint is the change in RV-to-LV ratio at 24 h after the procedure [16]. In the ongoing, randomized STRATIFY trial, 210 intermediate-to-high risk PE patients with a visible thrombus in the main, lobar, or segmental pulmonary artery at CT-scan will be randomly allocated to: (1) USAT (20 mg of alteplase over a 6-hour period) plus anticoagulation with unfractionated heparin (UFH) or low molecular weight heparin (LMWH), (2) low-dose systemic thrombolysis with 20 mg of alteplase over 6 h plus UFH or LMWH or (3) anticoagulation alone with UFH or LMWH. The primary endpoint is the reduction in the Miller obstruction index [22].

The ongoing HI-PEITHO trial is currently investigating USAT with EKOS plus anticoagulation versus anticoagulation alone in 406 intermediate-high-risk PE patients. The primary study endpoint is the composite of PE-related mortality, hemodynamic collapse, and PE recurrence within 7 days [23].

4.2.2. Mechanical thrombectomy

Mechanical thrombectomy encompasses thrombus-fragmentation techniques and aspiration embolectomy (Table 2).

4.2.2.1. Thrombus fragmentation. Various techniques, such as mechanical balloon fragmentation or motorized rotating pigtail catheters, have been developed to disrupt thrombi within the pulmonary arteries. Rotational pigtail thrombus fragmentation is technically non-demanding and widely available. Thrombus fragmentation and its subsequent migration into the distal pulmonary vascular system may lead to a reduction in pulmonary vascular resistance and RV afterload [24]. Two distinct thrombus fragmentation devices are used in practice: the Helix Clot Buster (Ev3 Covidien) and the Cleaner Rotational

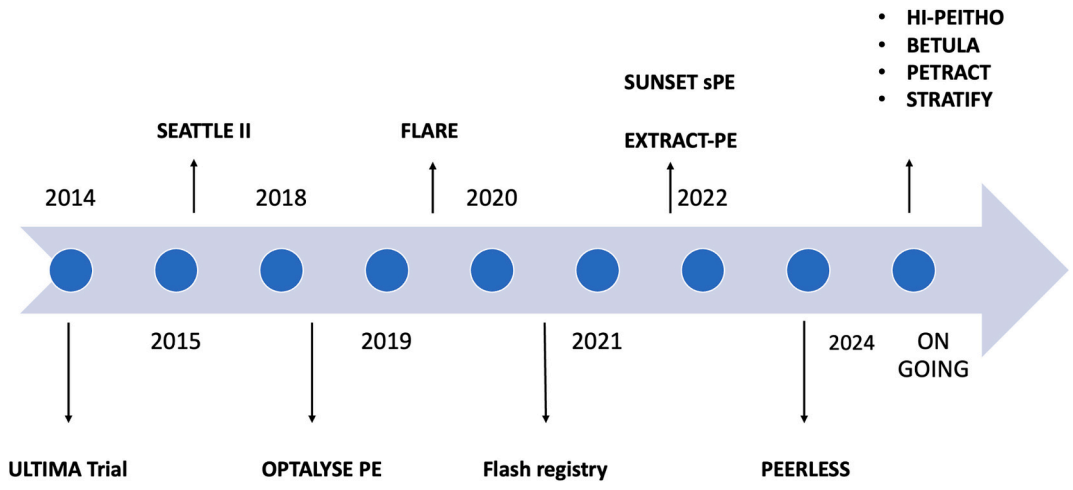

Fig. 4. Evolution of clinical trials over time and ongoing trials investigating novel interventional strategies for pulmonary embolism.

Table 2
Main features of clinical trials investigating systemic thrombolysis, CDT and mechanical thrombectomy in pulmonary embolism. Abbreviations: RV = right ventricle, LV = left ventricle, PAPs = systolic pulmonary artery pressure, CDT = catheter-directed thrombolysis, USAT: ultrasound-assisted thrombolysis, RCT = randomized clinical trial, PE = pulmonary embolism, OR = odds ratio, CI = confidence interval, rtPA = recombinant tissue plasminogen activator, LBMT = large bore mechanical thrombectomy, WR = win ratio.

Trial, year	Design	Inclusion criteria	Population	Intervention	Primary outcomes	Safety outcomes
Systemic thrombolysis						
BETULA, 2002	Randomized, double-blind study	Pulmonary hypertension or RV dysfunction, without shock	256 patients, intermediate-high PE	118 patients: heparin + alteplase 138 patients: heparin + placebo	In-hospital death or clinical deterioration higher in control group ($P = 0.006$)	No fatal bleeding or cerebral bleeding
PEITHO, 2014	Randomized, double-blind study	RV dysfunction + troponin I/T elevation	1006 patients, intermediate PE	Tenecteplase + heparin vs heparin	All-cause mortality and hemodynamic decompensation ad day 7: 5.6 % vs 2.6 % (OR 0.44, CI 0.23–0.87)	Major extra-cranial bleeding 2 % vs 0.2 %
Catheter-directed thrombolysis						
ULTIMA, 2013	Randomized controlled trial	RV/LV ratio ≥1.0	95 patients with intermediate PE	Heparin + USAT 10–20 mg recombinant tissue plasminogen activator over 15 h vs heparin	Mean decrease in RV/LV ratio from baseline to 24-h: 0.30 ± 0.20 versus 0.03 ± 0.16 ($P < 0.001$)	4 minor bleeding episodes (3 in USAT group, 1 in heparin group; $P = 0.61$)
SEATTLE II, 2015	Prospective, single-arm, multicenter trial	Proximal PE, RV-LV ratio ≥0.9	150 patients with acute massive (n = 31) or sub-massive (n = 119) PE	24 mg in situ t-PA for 24 h unilateral or 12 h bilateral	Mean RV/LV ratio (−0.42; $p < 0.0001$). Mean PAPs:51.4 vs. 36.9 mmHg; $p < 0.0001$); Miller Index score (22.5 vs. 15.8; $p < 0.0001$)	1 severe and 15 moderate bleeding events
SUNSET sPE, 2021	Multicenter, randomized, single blind trial	RV–LV ratio >1	81 patients, sub-massive PE	USAT vs standard catheter-directed thrombolysis	No significant reduction in pulmonary arterial thrombus reduction ($P = 0.76$)	2 major bleedings in USAT group
STRATIFY, 2019–2024 ongoing	Open-label, randomized trial	Intermediate-high risk PE	210 patients	1:1:1 randomization: 1) USAT with 20 mg of rtPA, Alteplase over 6 h + heparin, 2) iv 20 mg rtPA, Alteplase over 6 h + heparin; 3) heparin only	Reduction in Miller obstruction score index	Bleeding complications
HI-PEITHO, ongoing	Randomized controlled parallel-group comparison	RV dysfunction + positive cardiac troponin test + high risk of death/imminent haemodynamic collapse	406 patients with Intermediate-high risk PE	Standardized protocol of ultrasound-USAT anticoagulation vs anticoagulation alone.	The composite of PE-related mortality, cardiorespiratory decompensation, PE recurrence, within 7 days	Bleeding complications
Mechanical thrombectomy						
FLARE study, 2019	Prospective, single-arm	RV/LV ratio ≥0.9	106 patients with intermediate PE	Mechanical thrombectomy with FlowTriever System	48-h post-procedure, average RV/LV ratio reduction 0.38 (25.1 %; $p < 0.0001$).	6 major adverse events, 1 major bleeding
FLASH registry, 2022 ongoing	Prospective, multi-center registry	Acute intermediate or high-risk PE	800 patients, 77 % with intermediate-high risk PE	Registry of PE patients treated with mechanical thrombectomy using the FlowTriever System	−7.6 mmHg in mean PAPs (−23.0 %; $p < 0.0001$), + 0.3 L/min/m^2 in cardiac index (18.9 %; $p < 0.0001$). At 48 h, RV/LV ratio from 1.23 to 0.98, ($p < 0.0001$), severe dyspnoea from 66 to 16 % ($p < 0.0001$).	Major adverse events occurred in 1.8 % of patients, no device-related deaths
EXTRACT-PE, 2021	Prospective, single-arm, multicenter study	SBP ≥90 mmHg, RV/LV ratio >0.9	119 patients with acute PE	Treatment with Indigo aspiration system	Mean RV/LV ratio reduction from baseline to 48 h post-procedure 0.43 (95 % CI 0.38 to 0.47; $p < 0.0001$).	3 major adverse events
PEERLESS RCT, 2024	Randomized study	RV dysfunction + additional clinical risk factors	550 patients intermediate-high risk stable PE	Large-bore mechanical thrombectomy with the FlowTriever System vs CDT	LBMT had a lower occurrence of the primary endpoint (WR 5.01; 95 % CI: 3.68–6.97; $P < 0.001$) and fewer episodes of clinical deterioration or bailout (1.8 % vs. 5.4 %; $P = 0.04$). Postprocedural ICU utilization was significantly reduced with LBMT, including fewer ICU admissions (41.6 % vs. 98.6 %) and shorter stays exceeding 24 h (19.3 % vs. 64.5 %; both $P < 0.001$). There were no significant differences in mortality, intracranial haemorrhage, or major bleeding between the two strategies, nor in a secondary endpoint (WR 1.34; 95 % CI: 0.78–2.35; $P = 0.30$).	Procedural related adverse events

Thrombectomy System (Argon Medical Devices) [25].

4.2.2.2. Thrombus aspiration. Thrombus aspiration is achieved by applying suction through large bore catheters, inserted into a pulmonary artery and advanced proximally to the embolus. The catheter could be connected to a negative pressure pump such as the Indigo Aspiration system (Penumbra). Penumbra's Indigo Aspiration System includes the CAT12 and CAT8 catheters, optimized for mechanical thrombectomy in pulmonary embolism. Device choice depends on clot size, location, and patient anatomy [26].

Using the FlowTriever system (Inari Medical), the aspiration catheter (16, 20 or 24 Fr) is attached to a 60 milliliter aspiration syringe and/or with catheters with self-expanding nitinol discs [16]. The FLARE study, a prospective and single-arm study, demonstrated a 25 % reduction in CT-measured RV/LV ratio (from a 1.55 to 1.13 at 48 h post-procedure, $p < 0.0001$) with the FlowTriever system in 106 patients with intermediate-high risk PE. Additionally, the study showed improvements in the modified Miller score and pulmonary pressures [27].

The ongoing, prospective and multicenter FLASH registry aims at assessing the safety and efficacy of the second-generation FlowTriever device. Results from the initial 800 U.S.-based patients have been disclosed, revealing that around 8 % had high-risk PE, while 92 % had intermediate-risk PE (with 83 % falling into the intermediate-high-risk category). Approximately one-third of the participants had contraindications for thrombolytic treatment. Major adverse events were reported in 1.8 % of patients. The overall mortality rate was 0.3 % at 48 h and 0.8 % at 30-day follow-up. The investigators found a significant mean decrease of 7.6 mmHg in mean pulmonary artery pressure (−23.0 %; $p < 0.0001$) and a mean increase of 0.3 L/min/m^2 in cardiac index (18.9 %; $p < 0.0001$) [28].

The PEERLESS trial is a prospective, multicenter randomized controlled trial comparing large-bore mechanical thrombectomy (LBMT) with CDT in 550 patients with intermediate-risk PE with PESI class III–V or sPESI ≥1, documented RV dysfunction through echocardiography or CT-scan and elevated troponin levels [29]. LBMT met superiority over CDT for the primary endpoint, a hierarchal win ratio (WR) composite endpoint of all-cause mortality, intracranial haemorrhage, major bleeding, clinical deterioration or bailout, and postprocedural ICU utilization (WR 5.01, $P < 0.001$). The observed difference in the primary endpoint was mainly due to lower rates of clinical deterioration (1.8 % vs 5.4 %, $P = 0.04$), ICU admissions (41.6 % vs 98.6 %, $P < 0.001$), and shorter hospital stays (4.5 ± 2.8 vs 5.3 ± 3.9 days, $P = 0.002$) with LBMT. The ongoing PEERLESS II trial is currently investigating mechanical thrombectomy versus anticoagulation alone in 1200 patients with intermediate-risk PE [30].

The PE-TRACT study is an open-label, assessor-blinded, multicenter randomized trial designed to compare CDT plus anticoagulation with anticoagulation alone in 500 patients with intermediate-risk PE. The primary hypothesis is that CDT will improve peak oxygen uptake (peak VO_2) during cardiopulmonary exercise testing at 3 months and reduce New York Heart Association (NYHA) class at 12 months compared to anticoagulation alone. The two primary efficacy outcomes will be analyzed sequentially using a gatekeeping procedure, meaning that the NYHA class will only be compared if CDT is first shown to significantly increase peak oxygen consumption. In addition to efficacy, the study will also assess the safety and cost-effectiveness of CDT. By evaluating functional capacity and symptom burden over time, this trial aims to determine whether CDT provides long-term clinical benefits beyond standard anticoagulation in patients with intermediate-risk PE.

4.3. Pharmaco-mechanical thrombectomy

The AngioJet peripheral rheolytic thrombectomy catheter (Boston Scientific) is a pharmaco-mechanical thrombolysis device which facilitates CDT by delivering thrombolytic agents into the thrombus through power-pulsed injection and mechanically extracting the thrombus.

In a small single-center study ($n = 56$ patients with high-risk PE and contraindications to systemic thrombolysis), AngioJet treatment was associated with a hemodynamic improvements in terms of RV/LV ratio (from 1.33 ± 0.24 to 0.92 ± 0.18, $P < 0.01$) and PASP (from 56.7 ± 14.3 to 40.2 ± 13.4 mmHg) [31]. Some complications have been reported in literature in patients treated with the AngioJet catheter, including bradycardia, arrhythmia, hypotension and rarely haemoglobinuria associated with kidney failure. Importantly, a black box warning has been issued for AngioJet use for PE treatment in the United States. A summary of the main devices for interventional treatment of PE is shown in Table 3.

5. Advanced mechanical support: veno-arterial extracorporeal membrane oxygenation (VA-ECMO)

Extracorporeal veno-arterial membrane oxygenation (VA-ECMO) represents a viable temporary cardiopulmonary support for subjects experiencing acute cardiopulmonary failure before endovascular treatment. VA-ECMO rapidly reduces the afterload on the compromised RV ensuring effective cardiac output. In addition, VA-ECMO provides oxygenated blood reducing the risk of hypoxemia. In a large recent retrospective study enrolling patients with high-risk PE, standalone VA-ECMO was associated with higher mortality at 30 days compared with ECMO and reperfusion therapy combination (relative risk 1.47, 95 % CI 0.98–2.20; $P = 0.06$) [24]. In a recent retrospective study of 40 patients with high-risk PE treated with or without ECMO, patients who received immediate ECMO support had a lower risk of cardiac arrest ($P = 0.023$) and in-hospital mortality ($P = 0.036$) [32].

Due to the increased risk of haemorrhages and infections with prolonged circulatory support, the 2019 ESC guidelines on PE state that VA-ECMO may be considered in association with endovascular or surgical embolectomy for selected cases with refractory circulatory support or cardiac arrest (class of recommendation IIb, level of evidence C) [5]. A single-center study of 15 patients provided preliminary evidence for the use of large-bore embolectomy in patients under VA-ECMO (or in ECMO-stand-by), indicating that this approach is feasible und appears to be associated with high technical success. Nonetheless, patients should be carefully selected before offering VA-ECMO support in light of the high rate of in-hospital as well as long-term complications [33]. A large Australian study on ECMO used not only in the context of PE recently demonstrated that only one-third of patients were alive without major disability 6 months after ECMO treatment for high-risk PE [34].

6. A practical algorithm for CDT implementation in practice

For high-risk patients with PE, thrombolytic therapy (10 mg of alteplase bolus administered in 1–2 min, followed by 90 mg infusion over 120 min) should be administered concurrently with a continuous infusion of sodium heparin (Fig. 5). In case of persistent hemodynamic deterioration or in presence of contraindication to systemic thrombolysis, the PERT should be promptly activated (Fig. 5). While specific timeframes lack solid evidence, it's generally agreed that for patients already in centers equipped for CDT, CDT treatment should be started within 60 min. For patients requiring transfer to a CDT-capable center, treatment initiation within 90 min is preferred [25].

We provide below some illustrative clinical scenarios with corresponding treatment pathways:

- High-risk PE with absolute contraindication to thrombolysis: preferred treatment includes catheter-directed mechanical thrombectomy (e.g., FlowTriever) or aspiration embolectomy (e.g., Indigo), with consideration of adjunctive VA-ECMO if hemodynamic instability persists. A VA-ECMO strategy first should be considered in patients with advanced or protracted cardiogenic shock who are unlikely to respond to mechanical thrombectomy alone.

Table 3
Devices for interventional treatment of PE. Abbreviations: USAT, ultrasound assisted thrombolysis.

Device	EkoSonic®	PigTail	Indigo®	AngioJet®	FlowTriever®	Cleaner®
Mechanism	USAT	Rotational thrombectomy	Aspiration	Rheolytic thrombectomy	Aspiration	Rotational thrombectomy
Fragmentation	No	Yes	Yes	Yes	Yes	Yes
Aspiration	No	Yes	Yes	Yes	Yes	Yes
Local thrombolysis	Yes	No	No	No	No	No
Catheter dimensions	5 French	5 French	8–12 French	6–8 French	16–20–24 French	6–7 French
Complications	Bleeding, Perforation.	Bleeding, Perforation, Embolization.	Bleeding, Perforation, Embolization.	Bleeding, Acute renal injury, Emolysis.	Bleeding, Embolization, Perforation.	Bleeding, Embolization, Perforation.

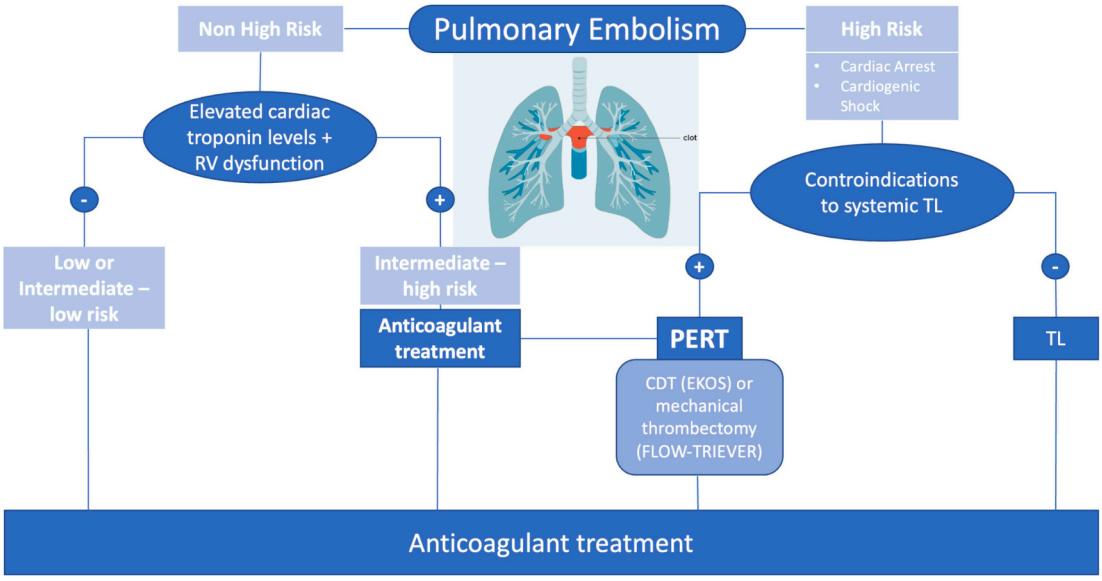

Fig. 5. A practical algorithm for patients with PE stratified by baseline risk. Abbreviations: CDT = catheter-directed thrombolysis; TL = thrombolysis; RV = right ventricle.

- Intermediate-high-risk PE with rapid clinical deterioration: in absence of contraindications to lysis, systemic thrombolysis should be considered; otherwise, USAT or CDT with reduced thrombolytic dose may be performed.
- Intermediate-high-risk PE with large clot burden but stable hemodynamic status: CDT or low-dose USAT should be considered, especially when RV dysfunction is significant and bleeding risk is low.
- Intermediate-risk PE in a center without interventional capability: Anticoagulation alone with close monitoring, and early transfer to a specialized center in case of clinical deterioration or persistent RV dysfunction.
- Recurrent PE despite adequate anticoagulation: Mechanical thrombectomy or combined CDT plus interventional support (depending on thrombus location and institutional resources) should be considered.

These clinical case scenarios underscore the importance of individualized treatments based on risk stratification, contraindications, and institutional capabilities. Systemic thrombolysis offers rapid reperfusion but carries the highest risk of major bleeding, especially in elderly patients and those with comorbidities. It remains the first-line treatment strategy in high-risk PE without contraindications. CDT allows targeted drug delivery with lower lytic doses, reducing bleeding complications. It is especially suitable for intermediate-high-risk PE with RV dysfunction and low bleeding risk. Mechanical thrombectomy provides a lysis-free approach and is preferred in patients with absolute contraindications to thrombolysis. It also allows immediate thrombus debulking in large central PE.

Institutional resources and operator expertise often guide the final decision; in centers with high interventional expertise, mechanical approaches may be preferred, while thrombolysis remains the mainstay in less-specialized settings. By incorporating these comparative considerations, PERT team can better tailor reperfusion strategies to individual patient profiles and local capabilities.

7. Long-term implications and post-thrombotic sequelae

A non-negligible proportion of patients may experience functional limitations after PE, including persistent dyspnoea, reduced exercise tolerance, and diminished quality of life (QoL)—a condition collectively referred to as post-PE impairment (PPEI) [36]. This chronic pulmonary dysfunction may affect up to 50 % of patients with PE, encompassing a clinical continuum of increasing severity, ranging from post-PE syndrome or chronic thromboembolic disease (CTED) to chronic thromboembolic pulmonary hypertension (CTEPH). CTED is defined by ongoing exertional dyspnoea despite the absence of resting pulmonary hypertension and is often linked to residual pulmonary vascular obstruction (RPVO) [37]. CTEPH represents the most severe manifestation of PPEI and is characterized by RPVO, resting pulmonary hypertension, and persistent dyspnoea—features that are associated with elevated morbidity and mortality [38]. Both CTED and CTEPH are linked to significantly impaired QoL and a poor long-term prognosis [37].

RPVO has been observed in up to 60 % of patients with PE treated by anticoagulation or thrombolytic therapy. Potentially, interventional strategies—such as mechanical thrombectomy—may mitigate the risk of RPVO and its sequelae, including CTED and CTEPH. Notably, the FLASH study reported a 6-month prevalence of 1.9 % for CTED and 1.0 % for

CTEPH, both lower than the historically reported CTEPH incidence of 2–4 % [31]. This reduced prevalence may reflect the benefits of early thrombus removal and subsequent prevention of RPVO.

Finally, it is important to distinguish between acute PE and acute-on-chronic PE, as their pathophysiology and treatment response may differ. CT findings as well as pulmonary pressure levels should be guide the differential diagnosis of acute PE and acute-on-chronic PE. In acute-on-chronic PE, vascular remodeling, collateral formation, and elevated pulmonary vascular resistance can limit the efficacy of thrombolysis and increase procedural risks during thrombectomy [39]. Therefore, reperfusion strategies should be carefully tailored in this subgroup, with consideration for early referral to specialized CTEPH centers.

8. Bleeding avoidance strategies

Due to the relevant prognostic impact of bleeding complications during and/or after the interventional management of PE, specific strategies to mitigate bleeding risk are paramount. These include:

- Vascular access site optimization: ultrasound-guided venous access is strongly recommended to minimize access-site complications, particularly in patients undergoing CDT or thrombectomy procedures.
- Dose adjustment of thrombolytics: Reduced-dose thrombolytic regimens in CDT to lower systemic exposure to fibrinolytic agents.
- Post-procedural monitoring of laboratory values: continuous monitoring of aPTT with a target therapeutic range between 50 and 75 s when using unfractionated heparin, alongside serial hemoglobin checks, and clinical surveillance for signs of occult bleeding.
- Post-procedural care: observation in monitored settings for at least 24 h, with periodic neurologic exams to detect potential intracranial bleeding, and early mobilization where feasible.

These strategies should be standardized across institutions to optimize procedural safety. In patients requiring VA-ECMO for hemodynamic deterioration due to PE, the management of thrombus remains particularly challenging. There are no established guidelines recommendations regarding the optimal therapy in patients supported with ECMO. A recent consensus document of the EAPCI, states that systemic thrombolysis is contraindicated in patients supported with ECMO [25].

Local low-dose thrombolysis should likely be avoided, as the minimum pulmonary perfusion required for effective drug delivery remains uncertain, and thrombolytic therapy inherently carries a significant risk of bleeding [25]. ECMO support combined with therapeutic anticoagulation may act as a bridge to definitive treatment with surgical or percutaneous pulmonary embolectomy, or, as documented in select cases, may facilitate spontaneous recovery [25].

However, in case of cardiac arrest presenting with asystole or pulseless electrical activity (PEA), patients on ECMO should be considered for systemic thrombolysis, given the potential benefits of this intervention [40].

The bleeding risk is significantly enhanced in patients receiving ECMO support. In this setting, mechanical thrombectomy has emerged as a potentially safer and more targeted approach, particularly when thrombolytics are contraindicated. Emerging evidence supports the feasibility of combining VA-ECMO with catheter-based thrombectomy as a bailout strategy in experienced centers. Nonetheless, the decision making process should be individualized, considering both bleeding risk and institutional expertise, and further studies are warranted to identify optimal reperfusion strategies under ECMO.

9. Challenges and potential barriers

Despite the growing evidence on novel interventional treatments for PE, several barriers still exist for a wider implementation in practice. These challenges are particularly relevant in resource-limited settings or non-tertiary hospitals. A major limitation is the restricted availability of interventional facilities and dedicated expertise, including catheter laboratories, interventional radiologists, or ECMO teams, which are often present in high-volume referral centers. In addition, the performance of catheter-directed thrombolysis or mechanical thrombectomy requires trained personnel with specific procedural skills.

Beyond technical constraints, logistical and organizational issues also play a key role. The success of a PERT model depends on a timely interdisciplinary collaboration among emergency physicians, cardiologists, radiologists, intensivists, and nursing staff. In the absence of streamlined communication protocols or institutional commitment, activation and coordination of PERT may be delayed or inconsistent. Moreover, the costs associated with specialized devices, staffing needs, and around-the-clock service availability may pose economic barriers, particularly where reimbursement policies are limited or inconsistent.

Finally, there is considerable variability in clinical protocols across institutions, and the lack of universal treatment algorithms may contribute to heterogeneity in patient management. Addressing these challenges requires not only technical solutions but also institutional commitment to multidisciplinary care pathways, education, and resource allocation. The development of scalable, pragmatic models for PERT implementation and interventional PE care is essential to extend the benefits of these therapies to a broader patient population.

10. Conclusions and future perspectives

Systemic thrombolysis is not infrequently contra-indicated in PE patients and even in those without formal contraindications, the bleeding risk (including intracranial haemorrhages) is concerning. Hence, this treatment is currently limited to high-risk PE patients, although it has mainly been investigated in intermediate PE patients. In the last decade, interventional strategies for PE have been developed for offering potentially faster and more effective restoration of hemodynamic conditions with a reduction of bleeding risk compared with thrombolysis. However, the comparative efficacy and safety of these strategies has been evaluated so far only in registries and small randomized studies.

Future research should investigate the effects of PE interventions in vulnerable and still neglected patient subgroups, including subjects with cancer, pregnancy, or recurrent PE. Furthermore, properly powered head-to-head randomized comparisons of CDT, mechanical thrombectomy, and systemic thrombolysis are still lacking. Studies assessing cost-effectiveness, operator learning curves, and long-term quality-of-life are also warranted. Finally, there is still paucity of data on the optimal thrombolytic dosing for CDT and potential biomarkers, which may support tailored reperfusion strategies.

CRediT authorship contribution statement

Gianluca Guarnieri: Methodology, Data curation, Conceptualization. **Antonio Landi:** Supervision. **Stefano Barco:** Investigation, Formal analysis. **Tiziano Cassina:** Data curation, Conceptualization. **Paolo Merlani:** Data curation. **Andrea Milzi:** Supervision, Formal analysis. **Roberta Petrino:** Writing – original draft, Methodology. **Elia Rigamonti:** Writing – original draft. **Daniel Sürder:** Writing – review & editing, Investigation. **Enrico Zucconi:** Visualization, Supervision. **Giovanni Pedrazzini:** Visualization, Validation. **Marco Valgimigli:** Supervision.

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Further reading

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